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Research Progress of Tissue Engineered Bone in Repairing Bone Defect

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Abstract: Bone transplantation has been used to repair bone defects for more than 300 years. Only in the United States, more than 1 million patients need bone grafting every year because of severe trauma, bone tumor, deformity and so on. Traditional bone graft materials include autogenous bone, allogeneic bone and artificial bone, but their wide application is limited because of various defects. With the development of biomedicine, tissue engineering and material science, the application of tissue engineered bone in the repair of bone defects has become a research hotspot.

Keyword: Stissue Engineered Bone, Bone Defect, Repair, Progress

Bone defect is a common clinical disease. Infection, tumor, trauma, surgical debridement of osteomyelitis[1] and various congenital diseases are the main causes of bone defect. The clinical methods of repairing bone defects include bone transplantation, artificial bone, bone tissue engineering and so on. Autogenous bone transplantation is the best method for the treatment of bone defects. However, the biggest problem of autogenous bone is that the source is limited, it is unable to repair large bone defects, and additional surgical trauma and operation time are increased. the shape and size of the transplanted bone are not easy to meet the requirements, and complications such as infection and pain occur in the bone removal area[2]. Allogeneic bone is rich in sources, but it has not been widely used because of religion, ethics, immune rejection and other reasons. Immune rejection after transplantation is the main reason that limits its application. Traditional artificial bone materials do not have bone induction; the slow absorption and degradation of materials affect the formation of new bone, so its application in the repair of bone defects is limited. With the in-depth study of scaffold materials, growth factors and stem cells, tissue engineered bone has been developed rapidly. at present, it has been used in clinical research, and gratifying results have been obtained. Tissue engineering bone materials not only have the advantages of traditional repair materials, but also improve their defects, such as mass preparation, no immunogenicity, shaping on demand, and will not cause secondary damage. Scaffolds, seed cells and bioactive factors are the three elements of tissue engineering[3, 4]. In this paper, the research progress of tissue engineered bone in repairing bone defects is reviewed.

Scaffold materials for bone tissue engineering

Scaffold is a part of bone tissue engineering. it is a kind of three-dimensional compatible structure which can simulate the performance of extracellular matrix and act as a template for cell adhesion and induce bone tissue formation[5-7]. It not only connects and supports cells and tissues, but also affects the morphology and phenotype of cells, controls cell proliferation, differentiation, and regulates cell movement, so scaffolds are an important part of bone tissue engineering. The scaffold materials used in bone tissue engineering are polymer materials, metal materials and ceramic materials. The polymer materials of bone tissue engineering scaffolds can be divided into two categories: natural polymer materials and synthetic polymer materials, in which natural polymer materials are the first biomaterials that can be found in nature, including chitin and its derivatives, collagen, alginate and so on. Collagen has been widely used in tissue engineering scaffolds and drug delivery carriers because of its good biocompatibility[8]. Although natural polymer materials have many advantages, such as excellent biocompatibility and degradability. However, there are also many defects, such as high cost and poor physical, chemical, mechanical properties and immunogenicity. Synthetic polymer materials can overcome these shortcomings. However, synthetic polymer materials have some problems, such as poor cell affinity, inflammatory reaction and so on. Metal materials: mainly include magnesium, titanium and their alloy materials. The mechanical properties and density of pure magnesium are similar to those of human bone, which can effectively reduce stress shielding after implantation, but its degradation rate is fast and produces a large amount of hydrogen, which is easy to harm the human body. The specific

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gravity of titanium is similar to that of human bone, but its strength is relatively low, so titanium alloy is usually used. The strength and toughness of metal materials are high, and casting will not reduce their strength. However, there are many problems after they are implanted into the human body. the implanted metal materials often do not work as expected. on the contrary, they have some side effects because of stress mismatch and bring great inconvenience to people's lives. Ceramic materials: mainly hydroxyapatite (HA), β-calcium phosphate (β-TCP), calcium phosphate cement (CPC) and bioactive glass (BG). Among them, hydroxyapatite is one of the main components of human bone, which has the best histocompatibility with bone, non-toxic and bone conductivity, and can guide bone tissue regeneration, but it is difficult to degrade in vivo, brittleness and low strength. The composition of β-calcium phosphate is similar to that of bone, and its degradation product is needed for new bone formation and is a satisfactory bone repair material, but β-TCP lacks bone-inducing activity. Calcium phosphate cement is composed of solid and liquid phases, which can be self-solidified at room temperature or in vivo. However, it produces heat after mixing with water, and the local temperature is as high as 70 ℃, which will kill the bone cells in the defect and degrade slowly. Bioactive glass is both osteoconductive and osteoinductive, which can release calcium and silicon ions to stimulate cells, activate related gene channels, induce rapid proliferation and differentiation of osteoblasts, stimulate angiogenesis and promote the rapid formation of new bone tissue.

Seed cell

There are two main sources of seed cells in bone tissue engineering: adult stem cells and embryonic stem cells ((hESC)). The outstanding representative is embryonic stem cell (hESC),. Since Reuhinoff BE[9] isolated the first hESC cell line, it is destined to be one of the promising seed cells in bone tissue engineering. Kim S et al[10] transferred embryonic stem cells into human rats through polyadenylate / hydroxyapatite scaffolds and successfully achieved osteogenesis in vivo. HESC has unlimited proliferation ability and totipotency. Making use of the characteristics of hESC, we can make it differentiate into osteoblasts and differentiate into vascular endothelial cells at the same time. After mixing them in an appropriate proportion, they are inoculated on the scaffold and then cultured and transplanted, so as to overcome the bone tissue engineering problem of constructing tissue engineering bone tissue while rebuilding its blood supply, and then improve the success rate of transplantation. The lateral differentiation ability of adult stem cells has been fully reflected in the osteogenic study of almost all extra-bone marrow mesenchymal stem cells[11]. Bone marrow mesenchymal stem cells (BM-MSCS) were studied earlier, but adipose mesenchymal stem cells (AT-MSCS) are favored by researchers because of their inconvenient materials and limited sources. Fibroblasts and osteoblasts come from mesenchymal cells, contrary to the scarcity of osteoblasts. Fibroblasts are widely distributed in bone tissue. With the development of the aging population, the number of most adult stem cells in the elderly is either generally reduced, and the differentiation potential is seriously decreased. At this time, fibroblasts are undoubtedly ideal seed cells.

Bioactive factors

At present, the main known bone growth factors are: transforming growth factor family (TGFs), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF), including BMP. According to their biological characteristics, different growth factors can be divided into four types according to their biological characteristics: BMP, TGF-13, bFGF, PDGF, VEGF and IGF promote the chemotaxis, proliferation and differentiation of target cells. BMP and IGF promote the synthesis of matrix in target cells. Related to angiogenesis include bFGF, VEGF and PDGF. The coupling of bone formation and bone resorption included TGF-B and IGF.

BMP is a hydrophobic acidic polypeptide with high affinity to hydroxyapatite and can only induce ectopic osteogenesis of bone tissue among many factors. This active protein chemotactic, aggregates and directionally differentiates undifferentiated mesenchymal cells into osteoblasts, and synthesizes collagen to promote the formation of bone matrix and form calcified bone tissue. 20 kinds of BMPS have been identified with BMP-2 as the center. BMP-2 is one of the most important osteogenic inducing factors among bone growth factors. Its main function is to induce mesenchymal cells to differentiate into osteoblasts and chondroblasts[12], forming a networked self-regulating osteogenic differentiation of bone marrow stromal cells[13]. BMP-2 has been approved for clinical use by FDA, so it has a certain representation in bone growth factors. The three conditions of osteogenesis induced by BMPs are inducing factor, target cell group and normal blood supply environment.

TGF-B is a family of protein peptides with multiple functions. TGF-B can promote the chemotaxis, proliferation, movement and aggregation of periosteal mesenchymal cells and osteoblasts, promote fibroblasts to secrete fibronectin and collagen, inhibit the activity of osteoclasts, and couple bone formation and bone resorption. At the same time, TGF-B can promote the production of extracellular matrix, induce bone regeneration and promote microangiogenesis, accelerate metabolism

and new bone formation[14]. TGF-B can activate and inhibit osteoblasts, which is biphasic to some extent.

Basic fibroblast growth factor(BFGF) was first purified from bovine nerve tissue by Gospodarowicz et al in 1974 and named bFGF. The target cells of BFGF are fibroblasts, vascular endothelial cells, chondrocytes, osteoblasts and so on. Its main biological functions are to promote neovascularization, promote the repair of soft tissue, cartilage and bone tissue, and promote limb regeneration[15].

Platelet derived growth factor(PDGF) is a kind of osteocyte mitogen and osteoblast chemokine, which can stimulate the synthesis of DNA and protein of osteocytes, promote the migration, recruitment, division, proliferation, differentiation and reconstruction of local blood circulation of bone forming cells[16].

Vascular endothelial growth factor(VEGF) is the most potent cytokine known to induce angiogenesis, also known as angiomodulin and vascular osmotic factor[17]. VEGF can promote endothelial cell proliferation and angiogenesis, regulate bone blood supply and participate in bone development and formation, and promote bone tissue regeneration and reconstruction by regulating the activity of osteoblasts and osteoclasts[18]. Studies have shown that cells far away from capillaries above 200pm can survive because of lack of nutrition and oxygen, thus it can be seen that vascularization is closely related to bone regeneration. The former can not only provide nutrition and oxygen, but also transport osteogenic progenitor cells, providing a good microenvironment for osteogenesis[19].

Insulin-like growth factors (IGF) regulates osteoblast growth, proliferation and bone matrix formation in the form of autocrine and paracrine, and mediates bovine growth hormone osteogenesis.

Problems and prospects

In view of the complex tissue structure and corresponding functions of bone tissue, it is difficult for a single material to meet the needs of bone tissue repair, and how to determine the amount of seed cells transplanted to the scaffold, how to improve the survival rate of seed cells after transplantation as much as possible, how to make the transplanted seed cells migrate from the transplant site to the damaged site as quickly as possible, and how to judge whether the seed cells have reached the target site. Whether the seed cells can differentiate directionally after reaching the predetermined site, how to improve the proportion of directional differentiation; whether the differentiated cells have sufficient osteogenic repair function; moreover, there is not a perfect seed cell for clinical large-scale application. After comprehensive consideration of the above points, in order to restore the shape and function of bone tissue to the maximum extent, in addition to continuing to develop new materials, the composite method is adopted to compound different kinds of biomaterials, and exogenous regulation and transformation of existing seed cells are adopted. Specific processing technology is adopted to develop biomaterials similar to autogenous bone tissue in mechanical properties, chemical properties, physical structure to promote the cure of bone defect.

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